UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/789,424	02/27/2004	Srinivasa Nagalla	39767-0003	5692

25213 7590 01/03/2007

HELLER EHRMAN LLP
275 MIDDLEFIELD ROAD
MENLO PARK, CA 94025-3506

EXAMINER	
DEJONG, ERIC S	
ART UNIT	PAPER NUMBER
1631	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/03/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/789,424	NAGALLA ET AL.	
	Examiner	Art Unit	
	Eric S. DeJong	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 September 2006 and 10 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-84* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-71,76 and 82-84* is/are rejected.

7)☒ Claim(s) *1,13,29,31,32,40,42,47,52,58,69,70 and 72-82* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *02/11/2005 and 07/21/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Election/Restrictions

Applicant's election of Group I (claims 1-84) in the reply filed on 09/26/2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Specification

The abstract of the disclosure is objected to because it contains more than 150 words. Further, line 3 of the abstract of the disclosure recites "sequences of molecules,. At least" and should be amended to recite --sequences of molecule. At least--. Appropriate corrections are required. See MPEP § 608.01(b).

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and /or amino acid sequences set forth in CFR § 1.821(a)(1) and (a)(2). See, for example, page 23, Table 3 and Figures 6, 7, and 10. However, this application fails to comply with the requirements of CFR § 1.821 through 1.825 because it lacks any submission of a computer readable form sequence listing, a paper copy for the specification, a statement under CFR § 1.821(f) and (g), and SEQ ID numbers cited along with each sequence in the specification or Figures. Applicants are also reminded that SEQ ID numbers are not required in the Figures per se, however, the

corresponding SEQ ID numbers then are required in the Brief Description of the Drawings section in the specification. Applicants are also reminded that a CD_ROM sequence listing submission may replace the paper and computer readable form sequence listing copies. Applicants are given the same response time regarding this failure to comply as that set forth to respond to this office action. Failure to respond to this requirement may result in abandonment of the instant application or a notice of a failure to fully respond to this Office Action.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. See, for example, paragraphs 0007, 0058, 0067, and 0073 of the instant specification. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required:

Claims 65, 67, 70 and 71 each recite the limitations "discriminating *de novo* sequences" and "non-discriminating sequences". The instant disclosure does not provide an antecedent basis for this claimed subject matter

Claim Objections

Claims 72-75 and 77-81 objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. See MPEP § 608.01(n). In the instant case, claim 72 depends from claims 71 and 1, claim 76 depends from claims 64 and 1, and claim 81 depends from depends from claims 76 and 81. Claims 73-75 and 78-80 are also included under this objection due to their dependence from claims 72 and 77, respectively. Accordingly, the claims 72-75 and 77-81 have not been further treated on the merits.

Claims 1, 13, 29, 31, 40, 42, 52, 69, 70, 76, and 82 are objected to because of the following informalities:

Regarding the form of the claims, MPEP § 608.01(m) states:

> "Each claim begins with a capital letter and ends with a period. Periods may not be used elsewhere in the claims except for abbreviations."

Claim 1 recites "a.", "b.", "c.", "d.", "e.", and "f." in lines 3, 5, 9, 12, 15, and 17, respectively, of said claim.

Claim 13 recites "a." and "b." in lines 2 and 3, respectively, of said claim. Further, claim 13, which depends from claim 1, recites the additional steps "a" and "b" (see lines 1 and 2 of claim 13) and should be amended to read as steps --g-- and --h--, respectively.

Claim 31 does not end with a period.

Claim 82 recites "a.", "b.", "c.", and "d." in lines 3, 5, 9, and 12, respectively, of said claim.

Claim 29 recites the limitation "breadth first search" (see line 1 of said claim) and should be amended to read as --breadth-first search--.

Claim 31 recites the limitation "breadth first search" (see line 1 of said claim) and should be amended to read as --breadth-first search--.

Claim 32 recites the limitation "breadth first search" (see line 1 of said claim) and should be amended to read as --breadth-first search--.

Claim 40 recites the limitation "1-or 2" (see line 2 of said claim) and should be amended to read as --1 or 2--.

Claim 42 recites the limitation "a specific molecules" (see lines 2 and 3 of said claim) and should be amended to read as --a specific molecule--.

Claim 47 recites the limitation "inserted into the in the mass-based alignment" and should be amended to read as --inserted into the mass-based alignment--.

Claim 52 recites the limitation "contains substitution matrix score" (see line 2 of said claim) and should be amended to read as --contains a substitution matrix score--.

Claim 58 recites the limitation "and that those mass objects" (see lines 3 and 4 of said claim) and should be amended to read as --and those mass object--.

Claim 69 recites the limitation "The method of claim 67, All matches between" (see line 1 of said claim) and should be amended to read as --The method of claim 67, wherein all matches between--.

Claim 70 consists of more than one sentence and recites "(original) This de novo sequence is then moved from the de novo sequence list to that sequence" in lines 4 and

5 of said claim. For the purpose of continuing examination, the second recited sentence following the recited term "(original)" has not been considered.

Claim 76 recites the limitation "The method of claim 64, a new sequence" (see line 1 of said claim) and should be amended to read as --The method of claim 64, wherein a new sequence--.

Appropriate corrections are required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-71, 76, and 82-84 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 82 each recite the limitation "producing at least one *de novo* sequence from mass spectrometry data of sequences of molecules" in lines 3 and 4 of the said claims. This causes the metes and bounds of the claims to be indefinite because it is unclear if the recited step of producing is limited only to an analysis of mass spectrometry data or, alternatively, requires performing an experimental mass spectroscopic analysis of at least one sequence so as to generate mass spectrometry data. Claims 2-71, 76, 83, and 84 are also included under this rejection due to their dependence from claim 1 (2-71 and 76) or claim 82 (claims 83 and 84).

For the purpose of continuing examination, the recited step of "producing at least one *de novo* sequence from mass spectrometry data of sequences of molecules" has been interpreted as requiring only to an analysis of mass spectrometry data.

Claims 1 and 82 each recite the limitations "molecules in the *de novo* sequence" and "molecules in each sequence" in lines 6-8 of the instant claims. This causes the metes and bounds of the claims to be indefinite as it is unclear how a single sequence can comprise a plurality of molecules. Similarly, the terminology of "sequence of molecules", "sequence of consecutive molecules", "single molecule", "molecules", "specific molecules", and "molecules in the sequence" recited through out the dependent claims of 2-71, 76, 83, and 84 suffers from the same above described issue of indefiniteness. For the benefit of applicants, amending the instant claims 1 and 82 to recite --fragments of the *de novo* sequence-- and --fragments in each sequence--, respectively, and amending the dependent claims to recite the terms --fragments-- and --fragment-- in place instantly recited terms "molecules" and "molecule" would be sufficient to overcome the instant rejection.

For the purpose of continuing examination, the limitations "molecules in the *de novo* sequence" and "molecules in each sequence" have been interpreted to read as fragments of the de novo sequence and fragments in each sequence, respectively. Further, the terms "molecules" and "molecule" recited in the dependent claims have been interpreted to read as --fragments-- and --fragment--, respectively.

Claims 65, 67, 70 and 71 each recite the limitations "discriminating *de novo* sequences" and "non-discriminating *de novo* sequences". This causes the metes and bounds of the instant claims to be indefinite because neither the instant claims nor the instant disclosure provide a definition for the recited terms. It is acknowledged that claim 67, which depends from claim 65, recites the limitation "wherein discriminating *de novo* sequences have the delta score greater than or equal to a delta threshold and non-discriminating *de novo* sequences have a delta score less than the delta threshold". However, it is unclear if the recitation of this limitation in claim 67 is intended to narrow the scope of the limitation "discriminating *de novo* sequences" and "non-discriminating *de novo* sequences" as recited in claim 65 or, alternatively, provide a definition for said limitations.

For the purpose of continuing examination, the limitation of "discriminating *de novo* sequences" is interpreted to be limited only to *de novo* sequences that have a delta score greater than or equal to a delta threshold value. Further the limitation of "non-discriminating *de novo* sequences" is interpreted to be limited only to *de novo* sequences that have a delta score less than said delta threshold value. Further, the instant specification is relied upon for the definition provided by the specification (see paragraph 0063) that teach a "delta score" is the difference between the scores of the first and second best alignments for given mass spectrum.

Claim 1 recites the limitation "the sequence in the sequence database" in lines 9 and 13 of the instant claim. There is insufficient antecedent basis for this limitation in

the claim because claim recites a plurality of "sequences in a sequence database" (see line 3 of the instant claim).

Claim 1 recites the limitation "the *de novo* sequence" in lines 10 and 14 of the instant claim. There is insufficient antecedent basis for this limitation in the claim because claim recites "producing at least one de novo sequence" (see line 6 of the instant claim).

Claim 12 recites the limitation "the sequence in the sequence database" in lines 1 and 2 of the instant claim. There is insufficient antecedent basis for this limitation in the claim.

Claim 13 recites the limitation "the sequence in the sequence database" in lines 3 and 4 of the instant claim. There is insufficient antecedent basis for this limitation in the claim.

Claim 19 recites the limitations "the *de novo* sequence" and "the sequence in the sequence database" in lines 2 and 3 of the instant claim. There is insufficient antecedent basis for these limitations in the claim.

Claim 27 recites the limitation "the sequence in the sequence database" in lines 2 and 3 of the instant claim. There is insufficient antecedent basis for this limitation in the claim.

Claim 28 recites the limitation "the next specified number" in line 3 of the instant claim. There is insufficient antecedent basis for this limitation in the claim.

Claim 31 recites the limitation "the breadth first search" in line1 of said claim. There is insufficient antecedent basis for his limitation in the claim.

Claim 32 recites the limitation "the breadth first search" in line1 of said claim. There is insufficient antecedent basis for his limitation in the claim.

Claim 32 recites the limitation "the sequence in the sequence database" in lines 3 and 4 of the instant claim. There is insufficient antecedent basis for this limitation in the claim.

Claim 33 recites the limitations "the *de novo* sequence" and "the sequence in the sequence database" in lines 4 and 5 of the instant claim. There is insufficient antecedent basis for these limitations in the claim.

Claim 34 recites the limitation "the sequence in the sequence database" in line 4 of the instant claim. There is insufficient antecedent basis for this limitation in the claim.

Claim 37 recites the limitations "the next molecule in the *de novo* sequence" and "the next molecule in the sequence in the sequence database" in lines 2 and 3 of the instant claim. There is insufficient antecedent basis for these limitations in the claim.

Claim 38 recites the limitation "the sequence in the sequence database" in line 3 of the instant claim. There is insufficient antecedent basis for this limitation in the claim.

Claim 41 recites the limitation "the modification information" in lines 1 and 2 of the instant claim. There is insufficient antecedent basis for this limitation in the claim.

Claim 42 recites the limitations "the modification information" and "the modification" in lines 1-3, and 6-8 of the instant claim. There is insufficient antecedent basis for these limitations in the claim.

Claim 44 recites the limitation "the modification" in lines 1 and 2 of the instant claim. There is insufficient antecedent basis for this limitation in the claim.

Claim 45 recites the limitations "the modification site" and "the modification" in lines 3, 5, and 6 of the instant claim. There is insufficient antecedent basis for these limitations in the claim.

Claim 46 recites the limitation "the sequence in the sequence database" in line 3 of the instant claim. There is insufficient antecedent basis for this limitation in the claim.

Claim 47 recites the limitations "the *de novo* sequence" and "the sequence in the sequence database" in lines 3 and 4 of the instant claim. There is insufficient antecedent basis for these limitations in the claim.

Claim 48 recites the limitations "the mass-based alignment", "the *de novo* sequence" and "the sequence in the sequence database" in lines 2 and 3 of the instant claim. There is insufficient antecedent basis for these limitations in the claim.

Claim 56 recites the limitation "the sequence in the sequence database" in line 3 of the instant claim. There is insufficient antecedent basis for this limitation in the claim.

Claim 57 recites the limitations "the molecules" in lines 1 and 2 of the instant claim. There is insufficient antecedent basis for this limitation in the claim.

Claim 58 recites the limitations "the *de novo* sequence" and "the sequence in the sequence database" in lines 2, 3, 5, and 6 of the instant claim. There is insufficient antecedent basis for these limitations in the claim.

Claim 59 recites the limitation "the sequence in the sequence database" in lines 2 and 3 of the instant claim. There is insufficient antecedent basis for this limitation in the claim.

Claim 60 recites the limitation "the *de novo* sequence" in lines 2 of the instant claim. There is insufficient antecedent basis for this limitation in the claim.

Claim 61 recites the limitation "the *de novo* sequence" in lines 1 and 2 of the instant claim. There is insufficient antecedent basis for this limitation in the claim.

Claim 62 recites the limitation "the *de novo* sequence" in lines 1 and 2 of the instant claim. There is insufficient antecedent basis for this limitation in the claim.

Claim 63 recites the limitations "the *de novo* sequence" and "the sequence in the sequence database" in lines 2 and 3 of the instant claim. There is insufficient antecedent basis for these limitations in the claim.

Claim 64 recites the limitations "the *de novo* sequence" and "the sequence in the sequence database" in lines 2 and 3 of the instant claim. There is insufficient antecedent basis for these limitations in the claim.

Claim 66 recites the limitation "the *de novo* sequence" in lines 2-4 of the instant claim. There is insufficient antecedent basis for this limitation in the claim.

Claim 67 recites the limitation "the delta score threshold" in lines 2-4 of the instant claim. There is insufficient antecedent basis for this limitation in the claim.

Claim 68 recites the limitation "the *de novo* sequence" in line 2 of the instant claim. There is insufficient antecedent basis for this limitation in the claim.

Claim 82 recites the limitation "the sequence in the sequence database" in lines 9 and10 of the instant claim. There is insufficient antecedent basis for this limitation in the claim.

Claim 82 recites the limitation "the *de novo* sequence" in lines 9 and 10 of the instant claim. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-71, 76, and 82-84 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1-71, 76, and 82-84 are drawn to a methods for identifying sequences of molecules and sequence modification from mass spectrometry data. The claimed method comprises the process steps of calculating at least one mass-based alignment, interpreting mass differences of modification sites, and calculating at least one match score, and, therefore, involves the application of a judicial exception. Regarding inventions involving the application of a judicial exception, said application must be a practical application of the judicial exception that includes either a step of a physical transformation, or produces a useful, concrete, and tangible result (State Street Bank & Trust Co. v. Signature Financial Group Inc. CAFC 47 USPQ2d 1596 (1998), AT&T Corp. v. Excel Communications Inc. (CAFC 50 USPQ2d 1447 (1999)). In the instant claims, there is no step of physical transformation, thus the Examiner must determine if the instant claims include a useful, concrete, and tangible result.

In determining if the claimed subject matter produces a useful, concrete, and tangible result, the Examiner must determine each standard individually. For a claim to

be "useful," the claim must produce a result that is specific, and substantial. For a claim to be "concrete," the process must have a result that is reproducible. For a claim to be "tangible," the process must produce a real world result . Furthermore, the claim must be limited only to statutory embodiments.

Claims 1-71, 76, and 82-84 do not produce a tangible result. A tangible result requires that the claim must set forth a practical application to produce a real-world result. This rejection could be overcome by amendment of the claims to recite that a result of the method is outputted to a display, a user, a readily accessible memory or other computer on a network, or by including a physical transformation.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-12, 63-71, 76, and 82-84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dancik et al. in view of Pevzner et al. (see IDS filed 02/11/2005).

The instant claims are drawn to a method for identifying sequences of molecules and sequence modifications from mass spectrometry data comprising producing at least one de novo sequence from mass spectroscopy data of sequences of molecules, calculating at least one mass-based alignment between each de novo sequence and sequence in a sequence database, molecular masses of molecules are compared to molecular masses of molecules of sequences contained in a sequence database, Interpreting mass differences of modification sites between sequences in said database and at least one de novo sequence that have been identified by the mass-based alignment as modifications identified in a modification catalog, and calculating at least one match score for the mass-based alignment for the mass-based alignment. Further claimed embodiments of the method comprises the steps of identifying sequences in the sequence database from mass-based alignments in response to the match score, and grouping identification of sequences from at least one de novo sequence into an identified macromolecule list that agrees with the mass.

Dancik et al. sets forth a review of de novo peptide and protein sequencing techniques via tandem mass spectrometry and the development of a software algorithm, SHERENGA (see Dancik et al., Abstract). Dancik et al. further sets forth that SHERENGA addresses an art recognized need for the previously unsolved computation

problems drawn to parameter learning, spectrum graphing, scoring schema, and sequencing algorithms (see Dancik et al., page 328, lines 24-45). Dancik et al. discloses methods for the identification of peptide and protein sequences using a tandem mass spectrometer capable of ionizing a mixture of peptides with different sequences and measuring their respective parent mass/charge ratios, selectively fragmenting each peptide into pieces and measuring the mass/charge ratios of the fragment ions (MS/MS spectra) and interpreting such MS/MS relies upon a data base searching (see Dancik et al., page 327, lines 1-11). Dancik et al. discloses that the automated SHERENGA further provides for improved *de novo* interpretation that automatically learns fragment ion types and intensity thresholds from a collection of test spectra generated from any type of mass spectrometer, wherein test data is used to construct optimal path scoring in the graph representations of MS/MS spectra and a ranked list of high scoring paths corresponding to potential sequences (see Dancik et al., Abstract and page 329, lines 1-27; page 330, lines 1 through page 333, line 9; and page 333, line 39 through page 336, line 5). Dancik et al. further disclose that peptides were obtained from in-gel or in-solution tryptic digestion of proteins isolated from yeast lysates, mouse plasma, and urine (see Dancik et al., page 338, lines 1-4). Dancik et al. further disclose an automated approach for scoring how well a candidate sequence "explains" a spectrum and then and selecting sequences that provide a best fit to a given spectrum. The disclosed scoring method relies upon an evaluation of probability that a given sequence P produces a given spectrum S via maximizing a probability function p(P,S) (see Dancik et al., page 334, line 19 through page 336, line 5). Dancik et al. further provides results

by the disclosed methods in Figures 5-9 (see Dancik et al. page 336, line 34 through page 337, line 20). Examples of interpretation with different quality are reflected by ambiguities in initial and/or terminal 1-3 amino acids (see page 336, line 34 through page 337, line 5). Dancik et al. further displays and labels mass objects relied upon to reflect different qualities of interpretation in Figure 10. To evaluate the performance of the disclosed de novo algorithms, Dancik et al. introduces the use of ladder difference metric between the predicted and actual sequences (see Dancik et al., page 337, lines 6-20).

While Dancik et al. sets forth the above discussed approaches to identifying sequences of molecules from mass spectrometry data, Dancik et al. does not fairly teach or suggest interpreting mass differences of modification between a sequence in a database and a de novo sequences that has been identified by mass based alignment as modifications in a modification catalog (see for example step (c) of instant claim 1).

Pevzner et al. sets forth methods drawn to efficient database searching for identification of mutated and modified proteins via mass spectrometry. Pevzner et al. further teach that the disclosed methods and algorithms address an art recognized need for algorithms that sort out reliable database hits from unreliable ones and identify mutated and modified peptides (see Pevzner et al., Abstract). Pevzner et al. further set forth that the disclosed approaches demonstrate advantages over known prior art methods and further demonstrate the use of a spectral alignment approach as a filter in a new database search algorithm that reliably identifies peptides differing by up to two mutations/modifications from a peptide in a database (see Pevzner et al., Abstract).

Figure 1 and Table 1 of Pevzner et al. list a plurality modified peptides used in the disclosed methods and is fairly interpreted to read on a modification catalog as instantly claimed. Further, Pevzner et al. rely upon MS/MS sequence methods to identify by mass based alignment to correlate sequence fragments to the modified peptides set forth in Figure 1 and Table 1 (see Pevzner et al., page 295, col. 2, line 43 through page 299, col. 1, line 15). Pevzner et al. further sets forth the application of spectral convolution of experimental and theoretical spectra that allow for the detection of mutations/modification without an exhaustive search (see Pevzner et al., page 292, col. 2, line 35 through page 294, col. 2, line 30). Figure 2 of Pevzner et al. further demonstrates the use of a set of differences matrixes, which are fairly interpreted as substitution matrixes, required to practice the spectral convolution procedures.

Therefore it would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains to use the disclosed methods for the identification of sequences using a tandem mass spectrometry, as set forth by Dancik et al., in combination with the methods drawn to efficient database searching for identification of mutated and modified proteins via mass spectrometry, as set forth by Pevzner et al., because Pevzner et al. teaches that the disclosed methods and algorithms address an art recognized need for algorithms that sort out reliable database hits from unreliable ones and identify mutated and modified peptides.

Claims 1-27, 63-71, 76, and 82-84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dancik et al. in view of Pevzner et al., as applied to claims 1-12, 63-71, 76, and 82-84 above, and further in view of Mann et al. (see IDS filed 02/11/2005).

The instant claims are drawn to a method for identifying sequences of molecules and sequence modifications from mass spectrometry data as set forth above. In further claimed embodiments the method comprises the steps of identifying a sequence in the sequence database with a tag match and generating a mass-based alignment between a de novo sequence and a sequence in the sequence database.

Dancik et al. in view Pevzner et al. provide for the above discussed methods of identifying sequences using a tandem mass spectrometry, as set forth by Dancik et al., in combination with the methods drawn to efficient database searching for identification of mutated and modified proteins via mass spectrometry, as set forth by Pevzner et al. However, neither Dancik et al. nor Pevzner et al. fairly teach or suggest identifying a sequence in a sequence database with a tag match (see for example, step (a) of instant claim 13).

Mann et al. demonstrate an approach to the identification of mass spectrometrically fragmented peptides (see Mann et al., Abstract). Mann et al. set forth that the disclosed methods as a means for interpreting complex tandem mass spectra by use of searching by peptide sequence tags (see Mann et al., page 4390, col. 2, lines 1-32). Mann et al. further demonstrate that MS/MS data can be relied upon for peptide identification with tags as short as two amino acids that can further be located in the presence of posttranscriptional modification or a sequence difference between the

measured peptide and the peptide database (see especially Mann et al., page 4390, col. 2, lines 23-31 and page 4393, col. 1, line 25 through page 4397, col. 2, line 3).

Therefore it would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains to use the disclosed methods for the identification of sequences using a tandem mass spectrometry, as set forth by Dancik et al., in combination with the methods drawn to efficient database searching for identification of mutated and modified proteins via mass spectrometry, as set forth by Pevzner et al., and in further combination with searching methods that rely on peptide sequence tags, as set forth by Mann et al., because Mann et al. teaches that the error tolerance of the peptide sequence tag approach is very high and is crucial in cases where predicted mass peptides is likely to be wrong (see especially, Mann et al., page 4398, col. 1, lines 22-37).

Claims 1-71, 76, and 82-84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dancik et al. in view of Pevzner et al. in view of Mann et al. as applied to claims 1-27, 63-71, 76, and 82-84 above, and further in view of Bader.

The instant claims are drawn to a method for identifying sequences of molecules and sequence modifications from mass spectrometry data as set forth above. In further claimed embodiments the method comprises generating mass-based alignment using a breadth-first search (see for example instant claim 28).

Dancik et al. in view Pevzner et al. in view of Mann et al. provide for the above discussed methods of identifying sequences using a tandem mass spectrometry, as set

forth by Dancik et al., in combination with the methods drawn to efficient database searching for identification of mutated and modified proteins via mass spectrometry, as set forth by Pevzner et al., and in further combination with searching methods that rely on peptide sequence tags, as set forth by Mann et al. However, neither Dancik et al., Pevzner et al., nor Mann et al. fairly teach or suggest generating mass-based alignment using a breadth-first search.

Bader sets forth methods related to extracting relevant complexes and pathways from high-throughput proteomics data sets to identify and extract networks are that essential to the art recognized problem of building pathways starting from known proteins of interest (see Bader, page 1869, col. 1, lines 1-10). Bader discloses the developed of an efficient algorithm, SEEDY, that extracts biologically relevant biological networks from protein–protein interaction data, building out from selected seed proteins. The algorithm relies on a previous study establishing statistical confidence levels for interactions generated by two-hybrid screens and inferred from mass spectrometric identification of protein complexes (see Bader, page 1869, col. 1, lines 11-25). Bader further discloses the evaluation of the disclosed algorithm by use of a breadth-first outward search based on an outward traversal of a protein interaction network (see Bader, page 1870, col. 2, lines 5-22).

Therefore it would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains to use the disclosed methods for the identification of sequences using a tandem mass spectrometry, as set forth by Dancik et al., in combination with the methods drawn to

efficient database searching for identification of mutated and modified proteins via mass spectrometry, as set forth by Pevzner et al., in combination with searching methods that rely on peptide sequence tags, as set forth by Mann et al., and in further combination with the use of a breadth-first outward search based on an outward traversal of a protein interaction network, as set forth by Bader, because Bader teaches that the disclosed breadth-first outward search is applicable to the analysis of an algorithms inferred from mass spectrometric identification of protein complexes.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. DeJong whose telephone number is (571) 272-6099. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

EDJ EDJ

John S. Brusca 24 December 2006

JOHN S. BRUSCA, PH.D
PRIMARY EXAMINER